FOOD AND DRUG ADMINISTRATION

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

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Now, what marker to use? Well, physicians use free T4. They also use TSH. If we were to use those, though, you would have to define the maximally accepted changes in TSH are to ensure the physicians of their therapeutic equivalence.

So to conclude, small differences matter. Products that differ by 12.5 percent cannot be detected with the current criteria, and we fully believe that we should bring all the scientific prowess in academia, FDA, endocrine societies, and industry to consider the issues of how to construct proper evaluation of bioequivalence in these T4 products.

That concludes my presentation.

DR. JOHNSON: Well, this part of the presentation will now focus on the FDA's current recommendation for evaluating levothyroxine sodium bioequivalence. However, before I begin, I want to make a couple of comments with regard to some of the slides that we just saw from Abbott Laboratories.

First of all, we want to thank Abbott Laboratories for conducting their correction method study. This data was confirmatory and very useful when the FDA decided to adopt a baseline correction method for evaluating levothyroxine sodium tablet bioequivalence.

However, there are some drawbacks with this

particular study design. The use of 400 and 450 microgram doses yielded thyroxine concentrations that were closer to baseline. This is problematic because it prevents an accurate evaluation of the true differences that exist between the two doses and this is likely due to some sort of baseline interference. That's why the agency has recommended in the guidance and continues to recommend that doses of 600 micrograms or greater are used.

Also the checkbox slide that compared the different evaluation methods clearly shows why TSH on its own is inappropriate. The point estimate was detecting a 24 percent difference when in actuality there was only a 12.5 percent real difference between the products.

Now on to the bioequivalence design. This is the current study protocol that we're recommending to sponsors seeking A-B ratings. A single-dose, two-way crossover study in which healthy subjects will receive 600 micrograms of both test and reference product. Pharmacokinetic analysis will be conducted using total thyroxine with a baseline correction.

Now, let me discuss some of the rationale behind the study design. First of all, the use of healthy subjects allows us to do a single-dose study and a single-dose crossover study is the most sensitive method for evaluating the true formulation differences between

products and that's really what we're looking at. A single-dose study cannot be conducted in patients. A 600 microgram dose in healthy subjects provides concentrations that are significantly higher than the individual subject's baseline T4 values, and the farther away from the baseline that you actually get, the more accurate the evaluation of the products. The issue of nonlinearity is really not an issue since the subject is receiving the same amount of drug in each treatment period.

Regarding the bioequivalence measures that have been discussed this morning, total thyroxine is the preferred measure for demonstrating bioequivalence. It can be accurately measured in vivo and is the drug that is being administered to the subject. T3, on the other hand, is merely an active metabolite, and the Food and Drug Administration does not use active metabolites for conferring bioequivalence, unless the active parent cannot be measured in vivo.

Finally TSH. TSH is a biomarker and it's an indirect measure. It's downstream from what is being administered and it's considerably more variable than thyroxine. It's also very easily influenced by other environmental factors, such as time of day and ambient temperature.

To kind of give you an idea of where each of

these measures fits into this negative feedback system, let's start with the lower left-hand corner, with the L-T4 or T4 inputs. Once you have conversion to T3, the T3 has an inhibitory effect on the hypothalamus which ultimately results in a reduction in the amount of TSH secretion from the anterior pituitary, but this is not a mutually exclusive event. As mentioned before, other factors influence the TSH values.

According to the Code of Federal Regulations, in descending order of accuracy, sensitivity and reproducibility for determining bioavailability and bioequivalence of a drug product, the best choice for evaluating bioequivalence is the concentration of the active ingredient and that's where T4 fits in. TSH, on the other hand, would be relegated to the third or fourth category.

As was made very clear in the previous presentation, using total thyroxine without a baseline correction is insensitive for conducting bioequivalence studies with levothyroxine sodium tablets and the FDA completely concurs. Rather, a baseline correction method whereby the mean of three pre-dose samples is subtracted from all of the subsequent post-dose samples. This is the preferred method and it is adequately sensitive for evaluating levothyroxine bioequivalence.

Now, when the agency decided to adopt a baseline correction method for bioequivalence, we went back to data from the six original NDA applications. Dosage from proportionality studies from four the six NDAs were re-evaluated using the baseline correction method and they're presented here.

Let me orient you to this slide. On the left-hand side, we have four products, 1, 2, 3 and 4. The first two columns are AUC and the second two columns are Cmax. This is a three-way crossover study. The dose that was used for the comparison was 600 micrograms, and as you can see, the bioequivalence criteria, when they're applied to these data sets, the confidence intervals still fall well within the confidence bounds of 80 to 125.

These results also show the power and sensitivity of this method because it shows the sensitivity to detect real differences as evidenced by the values circled in red. We've got a 14 percent increase in level 4, in product 4, for AUC, and on the same scale, we also have about a 9.5 percent decrease. The confidence limits, if this were slightly more variable, would have clearly failed.

In conclusion, the FDA has thoroughly reviewed each of the NDA applications that have come in. We've had a lot of data -- there were nine submissions -- the

literature and the recent correction methods study, and we've concluded the following. Levothyroxine can be evaluated in healthy subjects. A single dose crossover study is a preferred method for detecting the true differences between products. T4 is an appropriate and sensitive measure for this particular process, and a baseline correction method using the mean of three pre-dose samples is adequate when determining bioequivalence between two levothyroxine sodium products.

Thank you.

I'd now like to introduce Dr. Barbara Davit who will be speaking on potassium chloride.

DR. DAVIT: Thank you. I'm Barbara Davit, and I recently became the Deputy Director for the Division of Bioequivalence in the Office of Generic Drugs.

I'll be presenting some information today about baseline correction methods for endogenous compounds for which the Division of Bioequivalence has a fair amount of experience and that's potassium chloride.

I'll be discussing the design of potassium chloride bioequivalence studies that we've been implementing, the application of baseline correction methods to bioequivalence study data, the impact of baseline correction on bioequivalence study outcome, and to accomplish this, I have two cases to present, one in which